

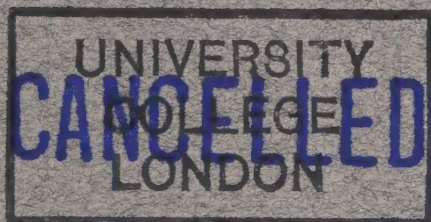
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VAGUS INHIBITION OF THE HEART IN ITS RELATION
TO THE INORGANIC SALTS OF THE BLOOD.

By W. H. HOWELL.

[FROM THE PHYSIOLOGICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY.]



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VAGUS INHIBITION OF THE HEART IN ITS RELATION TO THE INORGANIC SALTS OF THE BLOOD.

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IT is well known that an increase in the percentage of the neutral potassium salts, especially the potassium chloride, present in the blood or other circulating medium causes the heart to beat at a slower rate and eventually to come to rest in a condition of diastole, with loss of tone, just as in the case of vagus inhibition.¹ It is known also that this condition of potassium arrest is not the result of an immediately toxic action of the potassium salts on the tissues of the heart, since two observers, at least, have shown that simple removal of the excess of potassium salts, by diffusion for example, is followed by a recovery of the power of the heart to develop its normal rhythmic contractions.² The resemblances between the conditions of potassium inhibition and vagus inhibition have been noted by several observers,³ and have led some to suggest that the two phenomena are essentially identical.

On the other hand it has been shown by a number of observers, in experiments made chiefly on the hearts of cold-blooded animals, that an increase in the calcium salts in the circulating liquid leads to an augmented tonicity, an increased force and duration of the systolic contraction, and at times to an accelerated rate of beat.⁴ In

¹ For literature see BRAUN: Archiv für die gesammte Physiologie, 1904, ciii, p. 476, and HALD: Archiv für experimentelle Pathologie und Pharmakologie, 1905, liii, p. 227.

² MARTIN: American journal of physiology, 1904, xi, p. 370; BRAUN: *Loc. cit.*

³ BOTTAZZI: Archives de physiologie, 1896, p. 882; HOWELL: This journal, 1901, vi, p. 204; MARTIN: *Loc. cit.*

⁴ RINGER: Journal of physiology, iv, p. 29; v, 247; 1895, xviii, p. 425, etc.; HOWELL: *Loc. cit.*; LANGENDORFF and HUECK: Archiv für die gesammte Physiologie, 1903, xcvi, p. 473.

view of these facts the author was led to suggest some years ago that the inhibitory influence of the vagus and the augmenting influence of the sympathetic upon the heart may be exerted through some intermediate effect upon the potassium and calcium compounds in the heart tissue. With this general idea in mind an attempt has been made to determine experimentally to what extent the inhibitory influence of the vagus on the heart is affected by variations in the potassium and calcium contents of the circulating medium. The results of these experiments are reported in this paper.

The experiments were made upon terrapins and frogs. The heart was isolated, although left *in situ*. It was kept beating by means of a standard Ringer's solution which was supplied at constant pressure from a reservoir. The inflow cannula was inserted into one of the large veins opening into the heart, the other veins being ligated,¹ while the outflow from the ventricle was received through a cannula which was inserted into one of the aortæ and pushed through the valves so that its end lay freely in the ventricular cavity. In some cases the arterial cannula was omitted, the ventricle being allowed to empty itself through the stumps of the severed arteries. The contractions of the ventricle and the left auricle were recorded in most of the experiments, but in some cases registration was omitted in order to keep the heart free from the mechanical tension of the levers.

I. EFFECT OF VARYING THE AMOUNT OF POTASSIUM SALT IN THE CIRCULATING LIQUID.

The standard Ringer's solution used to irrigate the heart in this series of experiments had the following composition:

Sodium chloride	0.7	per cent.
Calcium chloride	0.023	" "
Potassium chloride	0.03	" "

The experiments were made upon terrapins. After the heart had been isolated and was beating regularly on the standard solution, it was submitted to the action of a series of liquids in which the percentage of potassium chloride varied from 0.01 per cent to 0.10 per cent, while the sodium and the calcium chloride were kept constant at

¹ Great care must be exercised in ligating the right superior cava in the terrapin, to avoid injury to the cardiac branches of the vagus. The ligatures must be laid as far as possible from the heart.

observed most distinctly in those hearts which for some reason exhibited an initial insensitiveness to vagus stimulation while under irrigation with the standard Ringer's mixture. In a number of cases hearts were found which before the operation were easily inhibited by stimulation of the vagus, but after isolation and while under irrigation with the standard mixture were inhibited with difficulty, that is, even maximal stimulation of the vagus caused only a slight slowing of the beat, or a short pause followed by a slowed beat. In such cases a slight increase in the potassium percentage made the heart very responsive to the action of the vagus, relatively slight stimuli causing complete diastole in all chambers for long periods.

This favorable influence of the potassium salts has, however, a distinct limit. When the percentage of the potassium chloride is increased to a point, 0.10 per cent or higher, at which it affects distinctly not only the rate, but the force or sequence of the heartbeats, the action of the vagus instead of being favored is markedly depressed. This result is observed in the phase just preceding the appearance of complete potassium arrest, at a time therefore when the potassium is sufficient to lower distinctly the efficiency of the heart contractions. It is not possible to state precisely at what concentration the depressing influence of the potassium on the vagus action begins, since different hearts react differently in this respect. As stated above, an increase to 0.07 per cent is associated usually with a distinct augmentation of the inhibitory influence of the vagus, while at 0.09 to 0.10 per cent the contrary effect may be noticeable. So long as the increase of the potassium constituent exercises no obviously weakening effect upon the heart it serves to increase its responsiveness to the action of vagus impulses. The depressing effect of large doses of potassium chloride upon vagus inhibition is similar to that shown by muscarin. At one stage in the action of this drug, when under its influence the beats of the heart are slowed, stimulation of the vagus has no effect upon the heart.¹

II. EFFECT OF REMOVAL OF THE POTASSIUM SALTS FROM THE CIRCULATING LIQUID.

The fact that an increase in the amount of diffusible potassium compounds in the heart favors inhibition, suggested naturally the possibility that, by supplying the heart with a circulating medium free

¹ WEINZWEIG: *Archiv für Physiologie*, 1882, p. 532.

from potassium, the amount of this element present in the heart in diffusible form might be reduced to such an extent as to suspend entirely the inhibitory action of the vagus. In the series of experiments carried out to test this idea both frogs and terrapins were used. The heart was isolated and kept beating by an artificial circulation of a standard Ringer's mixture. In the frog's heart it was found necessary, in order to obtain forceful efficient contractions, to add to the Ringer's mixture some sodium carbonate (0.003 per cent). The sensitiveness of the vagus was determined by finding the strength of induced current which sufficed to stop completely the contractions of the auricles or the ventricle. In the frog the combined vago-sympathetic trunk was stimulated, since stimulation of the intracranial portion of the vagus did not prove to be feasible under the conditions of the experiment. After ascertaining the sensitiveness of the heart to vagus stimulation the circulating liquid was changed from the neutral or alkaline standard Ringer's solution to one consisting of sodium chloride alone (0.7 per cent), or sodium chloride (0.7 per cent) plus calcium chloride (0.023 per cent). The effects of these two solutions may be considered separately.

Action of the sodium chloride (0.7 per cent). — When the heart is irrigated with an isotonic solution of sodium chloride the contractions of all chambers quickly become feeble, while the rate may be accelerated. All parts of the heart dilate greatly owing to loss of tone. The systole of the ventricle is especially incomplete, the contractions soon becoming restricted almost entirely to small movements at the base. While in this condition stimulation of the vagus may be entirely without effect upon the contractions of either the auricles or the ventricle. A similar observation has been reported recently by Wybau.¹ This author states that the loss of control of the vagus over the ventricle becomes apparent only after the ventricle has assumed an independent rhythm, and that to obtain this end, by his method, required an irrigation of the ventricle during some hours. In his method, however, the ventricle only was irrigated with the saline, by a perfusion cannula, the auricle and sinus receiving the animal's own venous blood. By the method that I used, the whole heart was irrigated with the solution of sodium chloride, and the condition of independence of vagus control developed within a few minutes, the auricle as well as the ventricle being entirely unaffected by vagus stimulation.

¹ WYBAU: Archives internationales de physiologie, 1904, ii, 198.

A similar experiment was described long ago by Schiff,¹ and later by Löwit,² who obtained the same results by the use of solutions of sodium sulphate and sodium carbonate. This latter observer used, however, concentrated solutions of these salts applied directly to the heart or injected into the lymph sinuses. If the exposure to the saline solution is not maintained for too long a period, a return to the standard Ringer's solution is followed by a reappearance of vagus inhibition, but if the irrigation with the sodium chloride solution is continued for a longer period, it may happen that a return to the Ringer's mixture, although followed by a revival of regular forceful beats in all chambers, is not accompanied by a return of vagus control. It seems probable, therefore, that the effect of solutions of sodium chloride on vagus inhibition is due in part to some injury to the endings of the vagus nerve in the heart, in addition to a possible direct action upon the heart muscle owing to a diffusion out of its potassium and calcium compounds. Wybau's generalization that the loss of vagus control is associated with an assumption of independent rhythmicity by the ventricle is not borne out by my experiments. The phenomenon appeared with this circulating medium when the heart beats, although feeble, showed a regular auriculo-ventricular sequence. For the sake of completeness it should be added that in some cases with the frog's heart, in which the irrigation was effected with a solution of sodium chloride made alkaline by sodium carbonate, the vagus inhibition was retained for a longer period, and in these cases the heart beats did not show the feeble incomplete contractions observed when the neutral saline was employed.

Action of a mixture of sodium chloride and calcium chloride (Ringer's mixture without potassium). — With this circulating liquid the heart continues to give vigorous beats. The first effect of the solution is usually to throw the heart into a condition of increased tone, this effect being especially marked upon the auricles which show a decided diminution in volume. The heart may also in the beginning exhibit quicker and more forcible contractions, but later the ventricular systoles become more prolonged, and a condition resembling partial or complete heart-block makes its appearance.

The ventricle responds to every second or third auricular contraction and finally may become entirely independent of the auricles,

¹ SCHIFF: Archives des sciences physiques et naturelles, 1877-78; also Recueil des mémoires physiologiques, 1894, i, p. 652.

² LÖWIT: Archiv für die gesammte Physiologie, 1881, xxv, 466.

or fall into a condition of irregular and infrequent beats. In the terrapin's heart the sodium calcium mixture sometimes causes the ventricle to assume an independent rhythm very abruptly, the beats changing at once from the rapid auricular rate to the slower ventricular rhythm and changing back again promptly when a Ringer's mixture containing potassium is passed into the heart. Whatever may have been the final effect upon the ventricle, and this varied in different animals, the result upon the auricles was uniform. After a preliminary augmentation of tone this portion of the heart continued to beat with regularity throughout the duration of the experiments lasting from a few minutes to one or two hours.

The effect of this sodium calcium mixture upon vagus inhibition of the ventricle of the terrapin's heart was clear and unmistakable. Stimulation of the vagus was entirely without effect upon the ventricular beats. The auricles might be inhibited and come to a complete standstill, but the ventricle continued to beat, with or without a brief preliminary pause, at its own slower independent rhythm. The simplest explanation of this uniform result is found in the suggestion made by Gaskell. According to this observer the vagus in the terrapin has no direct control over the ventricle. Ordinarily the ventricle stops when the vagus is stimulated because the auricles are inhibited, and consequently it receives no impulse from these chambers. Normal blood is not capable of stimulating the ventricle to an independent rhythm. When, however, the heart is irrigated with the sodium calcium mixture, the inhibition of the auricle while freeing the ventricle from auricular control, allows the potassium free circulating liquid to set up an independent ventricular rhythm. This explanation is supported by the results of experiments upon frogs. In the frog there is no doubt that the inhibitory fibres of the vagus control directly both the contractions of the ventricle and of the auricle. In accordance with this fact it was found that in this animal the auricle and ventricle behaved alike. If the sodium calcium mixture abolished vagus inhibition of the ventricle, it had the same effect on the auricle.

So far as the terrapin's heart is concerned, the true relation of the potassium compounds to the property of inhibition through the vagus is to be found in the reaction of the auricles, the part of the heart which is undoubtedly under the direct control of these nerves. The results actually obtained in the present series of experiments were not entirely uniform. In some of the experiments the contraction of

the left auricle was registered by attaching its tip to a lever, while in other cases in order to maintain entirely normal conditions both auricles were fully exposed, by cutting the arterial branches close to the ventricle, and were then simply observed. In a series of seven experiments upon terrapins made in the spring of 1905, it was found in all cases that the entire heart was completely inhibited with weak stimuli when irrigated with the standard Ringer's mixture (KCl 0.03 per cent). If the irrigating solution was changed to the sodium calcium mixture then, after a shorter or longer period, stimulation of the vagus with either weak or strong stimuli failed to arrest the auricle, or if any inhibitory effect was obtained, it was confined to the right auricle or was characterized by a long latent period, that is, the inhibition developed very gradually. On changing back to the standard Ringer's mixture complete and prompt inhibition of all chambers was readily obtained. In two similar experiments on the terrapin made in the fall of 1905, one heart when irrigated with the sodium calcium mixture gave complete inhibition of the auricles upon stimulation of the vagus, although the ventricle continued to beat. The stoppage of the auricles was, however, preceded by a long latent period (10 beats), the chamber during this period exhibiting a gradual dilatation from loss of tone. In the other heart, while on the sodium calcium mixture, stimulation of the vagus served only to weaken the beats of the auricles without bringing them completely to rest, the effect upon the right auricle being more distinct than that upon the left. In both cases a return to the potassium Ringer was followed by prompt complete inhibition of all chambers when the vagus was stimulated.

In a series of eight experiments upon frogs, also made in the fall (1905), less decided results were obtained. In four of these experiments the heart continued to give complete inhibition of all chambers when irrigated with the sodium calcium mixture, the inhibition being as prompt and complete as under normal conditions. In two of the other four experiments the heart showed at first complete inhibition of all chambers for a brief period, then the ventricle began to beat and was followed in order by auricle and sinus. That is, as long as the vagus was stimulated the heart showed a reversed rhythm, ventricle-auricle-sinus, which persisted for a short period after cessation of the stimulus and then suddenly changed to the normal sequence. A satisfactory explanation of this result is to be found in the fact that both the inhibitory and accelerator fibres were being stimulated,

and the action of the latter was favored while that of the former was depressed by the lack of potassium salts in the circulating mixture. Since the accelerator is known to influence the ventricle directly it may be that its action caused this chamber to beat first, and the ventricular systole was then followed in sequence by auricle and sinus, as happens usually when the ventricle is made to beat during vagus inhibition. In the other two experiments only the auricles beat well upon the sodium calcium mixture, and in the numerous stimulations made it was found that on the sodium calcium mixture the auricles could not be inhibited completely. If there was any cessation, it was only momentary and was followed at once by an escape. Return to a potassium mixture was accompanied by a complete and long-lasting inhibition whenever the vagus (left) was stimulated. It was observed, however, that after exposure to the sodium calcium mixture a return to the standard Ringer with 0.03 per cent potassium chloride gave no inhibition; to obtain this result, it was now necessary to raise the percentage to 0.05 or 0.07. It is evident from these experiments that the *direct inhibitory influence of the vagus upon the heart may be lost entirely when the circulating liquid contains no potassium salts, and that in such cases this influence is restored promptly by the addition of these salts in physiological amounts.*

The fact that in some cases, in the frog's heart, the vagus nerve inhibited all chambers of the heart, although potassium salts were not present in the circulating liquid, may be explained by assuming that in such cases the production of new potassium compounds in diffusible form took place in the tissue so rapidly that they could not be removed by diffusion with the circulating liquid. It is possible that a seasonal variation may enter as a factor in this regard. When one circulates a sodium calcium mixture through the heart, it is not probable that all the diffusible potassium compounds are thereby completely removed from the heart tissue. What is present in the tissue lymph may diffuse out promptly, but it is highly probable that more will be formed by dissociation of the relatively abundant supply of potassium material within the muscle. This consideration may explain the fact that in the different hearts examined different degrees of effects were obtained, varying from a complete loss of inhibition to a condition in which the action of the vagus was apparently unaffected. The significant cases certainly are those in which removal of potassium was followed by loss of power of inhibition, and in which this power was restored by the addition of potassium salts.

So far as our facts go at present, they warrant the probable conclusion that in the absence of diffusible potassium compounds in the substance of the heart muscle rhythmic automatic contractions may still persist, but the possibility of inhibition through the vagus nerve is removed.

III. EFFECT OF INCREASING THE AMOUNT OF CALCIUM SALT IN THE CIRCULATING LIQUID.

This series of experiments was carried out entirely upon terrapins. Beginning with the standard Ringer's mixture containing 0.023 per cent of calcium chloride, the calcium percentage was increased to 0.138 per cent through five stages (0.046, 0.069, 0.092, 0.115, and 0.138 per cent). The results from six experiments of this character were quite uniform. The end sought for was to determine the minimal stimulus applied to the vagus which was necessary at each concentration to cause complete inhibition of the auricles or the ventricle. So far as the ventricles were concerned it was found that as the calcium contents of the circulating liquid were increased inhibition became more difficult, that is, necessitated a stronger stimulus. At a certain concentration (0.10 per cent), which varied somewhat for the different hearts, complete inhibition failed entirely with the strongest stimuli, and in all probability stimulation of the vagus failed to have any effect upon the ventricle. That is to say, stimulation of the vagus under these conditions might be followed by a slower rate of the ventricular beats, while the auricle stopped completely in diastole. The slower rhythm of the ventricle was due probably, however, not to a direct inhibition, but to the fact that on stoppage of the auricles it began beating at once with its own slower rhythm on account of the higher concentration in calcium salts, a condition which, as is well known, develops an independent automatic rhythmicity in the ventricle of this animal. On the basis of these experiments we may conclude, therefore, that *as soon as the concentration of calcium salts in the circulating liquid is sufficient to develop an independent beat in the ventricle, vagus stimulation ceases to have any effect upon this part of the heart.*

The conclusion applies only to those ventricles upon which the vagus has little or no direct influence. Gaskell's statement that in the reptilian heart the vagus has no direct effect upon the ventricle and can influence its beat only through an effect upon the auricle is

in accord with all of my observations, except perhaps one. In one experiment, while irrigating the heart with the standard Ringer's mixture, both auricles and ventricle were inhibited completely by stimulating the vagus with a current strength of 75. The same result was obtained with a concentration in calcium chloride of 0.046 per cent, but at a concentration of 0.069 per cent the auricle alone was completely inhibited by a strength of 75, while the ventricle showed only a slowing of rate. On increasing the strength of stimulus, however, to 300 the ventricle as well as the auricles was brought to a complete stop. With higher concentrations of calcium chloride the ventricle could not be inhibited completely with any strength of stimulus, but assumed simply its slower independent rhythm, as described above. This experiment would indicate that the vagus may have, in some individuals at least, some direct connection with the ventricular muscle, although its influence upon this part of the heart is obviously less complete than in the case of the auricles.

With regard to the auricles quite a different result was obtained. With all concentrations of calcium chloride used the auricles were completely inhibited upon stimulation of the vagus, and, indeed, the minimal stimulus necessary to produce this effect remained unchanged throughout. We may conclude therefore that *so long as the concentration of the circulating liquid in potassium and sodium salts remains within normal limits, variations in the calcium salts (0.023 per cent to 0.138 per cent calcium chloride) have no influence upon the vagus inhibition of the auricles.*

THEORETICAL.

The very great and indeed essential importance of the inorganic salts to the normal properties of heart-muscle has been abundantly demonstrated within recent years. The facts that have accumulated force us to believe that the normal functions of the protoplasmic material of the heart depend upon the presence of a certain number of these salts, particularly those of sodium, potassium, and calcium, in certain definite proportions, and we cannot escape the conviction that these salts or their ions form compounds with the complex organic substances in the heart-tissue, compounds which perhaps may be regarded as addition products, and which are capable of dissociation.

From the experiments given above it would appear that vagus inhi-

bition of the heart is not possible when the tissue-lymph is depleted of its diffusible potassium salts, under conditions which ensure the retention of the other salts essential to normal activity. This fact, or probable fact, may be understood if it is assumed that the substance whose dissociation and oxidation yields the energy of contraction forms with the potassium salts a relatively stable compound, or at least has its property of dissociation prevented in some way by the presence of potassium salts, and that this action of the potassium constitutes the initial cause of inhibition. The analogy between the inhibition produced by excess of potassium salts in the circulating liquid and that caused by the stimulation of the vagus nerve is most striking,¹ and now that it appears that potassium salts in excess within certain limits favor vagus inhibition, while their absence or serious diminution in quantity retards or altogether prevents the inhibitory action of the vagus, it seems justifiable to assume as a provisional hypothesis that vagus inhibition takes place because the nerve impulses effect a sudden increase in the amount of diffusible potassium compounds in the heart-substance. We know from the work of Macallum² and others that the heart contains an abundant supply of potassium. This material is contained in organic combination, but probably as a compound that is capable of dissociation with the liberation of potassium. The possibility of the existence of such compounds and of their dissociation is indicated by the recent microchemical work of MacDonald³ upon the nerve fibre. It is quite conceivable therefore that the action of the vagus impulses consists primarily in augmenting such a dissociation and thus setting free an inhibitory substance, namely potassium, the presence of which, in excess of its usual amount, prevents the dissociation of the so-called contractile substance. Among the theories advanced to explain the

¹ It is sometimes stated that arrest of the heart by potassium differs from vagus inhibition in the fact that in the latter condition the heart is still responsive to external stimuli, while in the former it is not. MARTIN has shown, however, that with a dose of potassium chloride sufficient to stop the ventricle, this chamber may still be irritable to mechanical stimuli. On the other hand, LANGENDORFF states that muscarine applied directly to the heart destroys its irritability toward external stimuli, while ECKHARD, SCHIFF, and GASKELL have shown that stimulation of the vagus may also weaken or suspend the irritability of the heart.

² MACALLUM: *Journal of physiology*, 1905, xxxii, p. 95.

³ MACDONALD: *Journal of physiology*, 1905, xxxii, *Proceedings of the Physiological Society*, also *Proceedings of the Royal Society, London*, 1905, B, lxxvi, p. 322.

phenomenon of inhibition, that proposed by Gaskell¹ and Hering has found most favor among physiologists, or at least is most frequently referred to. According to Gaskell the inhibitory fibres of the vagus constitute an anabolic nerve to the heart-muscle, that is, its impulses cause an increase in the anabolic or assimilatory processes within the muscle. In favor of this view it has been urged that as an after-effect of vagus stimulation there is an increase in the force of the heart-beat and in the conductivity of the tissue, and, moreover, that during vagus inhibition the part of the heart affected shows an increased positive potential with reference to an injured area. In regard to the increase in the force of the heart beat observed after vagus inhibition, it must be remembered that this phenomenon is exhibited by the ventricle of the terrapin, and yet according to Gaskell this part of the heart in this animal is not actually inhibited, it simply comes to rest because the auricle is inhibited. It would seem from this that an increase in the force of contraction may follow a condition of rest, that is, absence of catabolism, and cannot therefore be cited as a proof of an increase in anabolism due to external influences.

As a matter of fact, we recognize in the inhibited heart muscle only a condition of suspended activity, a prolonged diastole, during which there is no evidence of disassimilation or physiological oxidations. It is somewhat difficult to conceive in the first place how a nerve impulse can lead to an increase in the assimilatory processes, but, granting that it may, it is not clear why such a condition should be accompanied by a cessation of catabolism. In other organs, such as the glands, an increased catabolism during activity goes hand in hand with a greater anabolism, and conditions, such for instance as a higher temperature, which may augment the anabolic activity of the living substance increase also the extent of the catabolic changes. This effect we should expect on the usual assumption that anabolism is essentially a synthetic process, whereby more complex and more unstable compounds are formed. The heart, however, may be inhibited in the cold-blooded animals during many hours. To suppose that during such long periods anabolic processes are proceeding continuously, to the exclusion of all catabolic changes, is to imagine a process of synthesis or polymerization of a practically indefinite extent. With regard to the argument that the muscle during inhibition shows an increased positive potential and therefore must be in a state of anabolism,

¹ GASKELL: Philosophical transactions, London, 1881, clxxiii, p. 1029.

because during catabolism there is the opposite condition of negative potential, it is of course easy to point out that the logic of the reasoning is not entirely sound. From the standpoint of physical chemistry the acquisition of an electrical charge implies a process of dissociation and formation of ions, and if anabolism consists, as is usually assumed, in the synthetic combination of certain unsaturated groupings, it should result in the production of electrically neutral compounds. According to the theory proposed in this paper, the vagus impulses, like those of motor nerves, set up a dissociation with the liberation of electrolytes in an ionized condition. It is assumed that the electrolyte in question is a potassium compound which acts as an inhibitory substance toward the energy yielding material. Upon this assumption we may understand the production of a positive potential, if, with Oker-Blom, we suppose that the kations of the potassium compounds diffuse more rapidly than the anions. This latter observer, in fact, has shown¹ that when one end of a fresh, uninjured sartorius muscle is treated with water or dilute solutions of potassium chloride, the end so treated becomes electro-positive to other parts of the muscle. He explains this result on the theory that a dissociation results with the liberation of electrolytes, and a more rapid migration of the positively charged ions through the surrounding sheaths. The work of Langley² and of Erlanger³ make it highly probable that there is no qualitative difference between the impulses transmitted by motor and inhibitory fibres, since a motor nerve, when led down an inhibitory path, continues to give inhibition. In the case of the heart the difference in action between the inhibitory and accelerator fibres must be referred in the long run to the fact that they end in different structures or substances. Histological work, it is true, does not support such a view, and on the chemical side our knowledge of the heart metabolism is far too meagre to justify any detailed hypothesis, but the physiological facts known regarding cardiac inhibition are in accord with the idea that the vagus fibres end in what might be designated as an inhibitory substance, which, under the influence of its impulses, is dissociated with the liberation of potassium compounds to which the phenomenon of inhibition is directly due.

¹ OKER-BLOM: *Archiv für die gesammte Physiologie*, 1901, lxxxiv, p. 191.

² LANGLEY: *Journal of Physiology*, 1904, xxx, p. 439.

³ ERLANGER: *This journal*, 1905, xiii, p. 372.

CONCLUSIONS.

In a circulating medium containing only sodium, potassium, and calcium chlorides

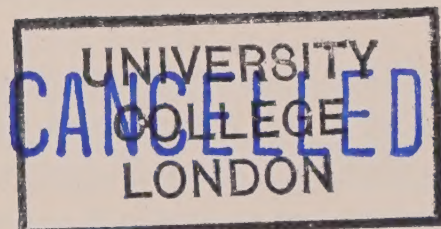
1. An increase in the amount of the potassium salt augments the sensitiveness of the heart to vagus inhibition, until the amount of the potassium becomes sufficiently large to cause itself marked inhibitory effects. Under the last condition the effect of vagus inhibition is greatly lessened.

2. Complete lack of potassium salts is attended by a diminution in, or entire loss of, vagus control of the different chambers of the heart.

3. A solution containing only sodium chloride (0.7 per cent) causes loss of vagus control of the heart-beats.

4. An increase in the calcium salts (0.023 to 0.138 per cent) has no effect upon vagus inhibition of the auricles. The same change is followed by diminution and finally entire loss of vagus action on the ventricle (terrapin), owing probably to the development of an independent ventricular rhythm.

5. The results of the experiments are interpreted to indicate that inhibition of the heart depends upon the presence of diffusible potassium compounds in the heart tissue, and that the vagus impulses act indirectly by increasing the amount of potassium compounds of this character.





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